Cymbalta® (duloxetine HCl) Medical Summary
New Information*

***NOTE: Per the Montana DUR Board *General Procedures for Public Comment* guidelines, information provided will focus on new information (including new indications, new studies excluding placebo-controlled studies, and new safety information) since June 28, 2006.**

I. NEW INDICATIONS: Generalized Anxiety Disorder (GAD)*

Indications and Doses – GAD

- Cymbalta, a selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SSNRI), received approval for the treatment of patients with Generalized Anxiety Disorder (GAD) in 2007. It is also indicated for the treatment of Major Depressive Disorder (MDD) and Diabetic Peripheral Neuropathic Pain (DPNP).[1]
- For GAD, while 120 mg/day has been shown to be effective, there is no evidence that doses higher than 60 mg/day confer additional benefit.[1]

Efficacy – GAD

- In individual and pooled studies, efficacy of Cymbalta in the treatment of generalized anxiety disorder (GAD) was established in one 9-week fixed-dose (60 mg/day and 120 mg/day) and two 10-week flexible-dose (60-120 mg/day) trials in adults.[1,2]
- In all 3 studies, Cymbalta demonstrated superiority over placebo as measured by the greater improvement in the Hamilton Anxiety Scale (HAM-A) total score (primary measure) and by the Sheehan Disability Scale (SDS) global functional impairment score (secondary measure). The SDS is a patient-rated scale that assesses impairment in three domains: work/school, social life, and family/home management responsibilities.[1,3]

Commonly Observed Adverse Events – GAD

- In GAD premarketing clinical trials (N=668 vs. 495), the most commonly observed adverse events (≥5% and at least twice placebo) for Cymbalta vs. placebo were: nausea (38% vs. 10%), fatigue (13% vs. 5%), dry mouth (12% vs. 4%), somnolence (12% vs. 3%), constipation (10% vs. 3%), insomnia (9% vs. 4%), decreased appetite (8% vs. 3%), hyperhidrosis (7% vs. 2%), decreased libido (7% vs. 2%), vomiting (5% vs. 2%), delayed ejaculation (5% vs. 1%), and erectile dysfunction (5% vs. 1%).[1]

Overall Discontinuation Rate Due to Adverse Events – GAD:

- In GAD premarketing placebo-controlled trials, the overall discontinuation rate due to adverse events was 16% (Cymbalta) vs. 4% (Placebo). Nausea (3.7% vs. 0.2%), vomiting (1.4% vs. 0%) and dizziness (1.2% vs. 0.2%) were the common adverse events reported as reasons for discontinuation and considered to be drug related. [1]

II. NEW STUDIES: Major Depressive Disorder*

***Duloxetine vs. Lexapro:*[4]**

(Efficacy & Safety: Major Depressive Disorder Placebo-Controlled Comparative Study – published 2007)

- Cymbalta 60 mg once daily demonstrated an onset of sustained clinically meaningful improvement at least as fast as (non-inferior to) Lexapro 10 mg once daily.[4] The HAMD-17 remission rate at 8 weeks of fixed dose treatment was 40% for Cymbalta and 33% for Lexapro, a difference that was not statistically significant. (p.=.25), and there were no significant differences in efficacy between the treatments at 8 months after 6 more months of open titration.
- In the Cymbalta-Lexapro study, nausea, dry mouth, vomiting, yawning, and irritability occurred significantly more frequently among Cymbalta-treated patients compared to Lexapro- and placebo-treated patients, in addition decreased appetite, increased sweating, anorgasmia and sedation occurred more frequently in Cymbalta-treated patients compare to placebo-treated patients. The rate of discontinuation due to AEs was similar for each group, placebo 5.8%, Cymbalta 7.3%, and Lexapro 5.1%.[4]

***Duloxetine vs. Effexor XR:*[5]**

(Efficacy & Safety – Major Depressive Disorder Comparative Study – published 2007)

- Cymbalta 60 mg once daily and Effexor XR 150 mg once daily had similar (not superior) Global Benefit Risk Assessment scores at six weeks (the primary outcome measure). Both Cymbalta and Effexor XR demonstrated substantial antidepressant efficacy as measured by the $HAMD_{17}$ total score.[5]
- In the Cymbalta-Effexor XR studies, the most common AEs (> 10%) were nausea, headache, dry mouth, constipation, increased sweating, dizziness, diarrhea, insomnia, somnolence, and decreased appetite and Cymbalta-treated patients reported significantly more nausea and dizziness than Effexor XR-treated patients. 12% of Cymbalta-treated patients discontinued due to Adverse Events compared to 6% of Effexor XR-treated patients.[5]

III. Important Safety-Related Label Changes since June 2006:**
(**Full safety information can be found in the attached Cymbalta package insert.)

Clinical Worsening and Suicide Warning:[1]

- Suicidality and Antidepressant drugs – Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients.

Other Warning/Drug-Drug Interactions: [1]

- Development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs, including triptans, and drugs which impair metabolism of serotonin (including MAOIs).

Precautions: [1]

- As with other antidepressants, Cymbalta has been associated with cases of clinically significant hyponatremia that appeared to be reversible when Cymbalta was discontinued.[1]
- Orthostatic hypotension and syncope have been reported with therapeutic doses of Cymbalta. Consideration should be given to discontinuing Cymbalta in patients who experience symptomatic orthostatic hypotension and/or syncope.[1]
- In the 12-week acute treatment phase of the diabetic peripheral neuropathic pain (DPNP) studies, HbA_{1c} was stable in both Cymbalta and placebo-treated patients. In the extension phase of these studies (up to 52 weeks), an increase in HbA_{1c} in both the Cymbalta and the routine care groups was noted, but the mean increase was 0.3% greater in the Cymbalta group.[1]

References

1. Duloxetine hydrochloride full Prescribing Information. Indianapolis, IN: Eli Lilly and Co; 2007.
2. Allgulander C, Hartford J,Russell J, Ball S, Erickson J, Raskin J, and Rynn M. Pharmacotherapy of generalized anxiety disorder: results of duloxetine treatment from a pooled analysis of three clinical trials. CMRO Vol. 23, No. 6, 2007, 1245–1252
3. Endicott J, Russell JM, Raskin J, Detke MJ, Erickson J, Ball SG, Marciniak M, Swindle RW. Duloxetine treatment for role functioning improvement in generalized anxiety disorder: three independent studies. Journal of Clinical Psychiatry. 2007; 68:518-524.
4. Nierenberg AA, Greist JH, Mallinckrodt CH, Prakash A, Sambunaris A, Tollefson GD, Wohlreich MM. Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a noninferiority study. Current Medical Research and Opinion. 2007; 23(2):401-416.
5. Perahia DGS, Pritchett YL, Kajdasz DK, Bauer M, Jain R, Russell JM, Walker DJ, Spencer KA, Froud DM, Raskin J, Thase ME, A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. Journal of Psychiatric Research.